REMARKS

Claims 28-34 are pending. No amendments have been made by way of the present submission. Thus, no new matter has been added. Additionally, no new issues have been raised by way of the present submission which would require additional search and/or consideration on the part of the Examiner.

In the event that the present submission does not place the application into condition for allowance, entry thereof is respectfully requested as placing the application into better form for appeal.

In view of the following remarks, Applicant respectfully requests that the Examiner withdraw all rejections and allow the currently pending claims.

Issues under 35 U.S.C. §103(a)

The Examiner has rejected claims 28, 29 and 32-34 under 35 U.S.C. §103(a) as being obvious over Nakagawa et al., USP 5,142,647 (hereinafter referred to as Nakagawa '647) in view of JP 07-133225 (hereinafter referred to as JP '225).

The Examiner has also rejected claims 30 and 31 under 35 U.S.C. §103(a) as being obvious over Nakagawa '647 in view of JP '225, further in view of JP '225 in view of Kitagawa (Japanese Journal of Pharmacology, 1989, Vol. 49, suppl. pp. 281 (hereinafter referred to as Kitagawa).

Applicant respectfully traverses each of the above rejections.

The Present Invention and Its Advantages

Independent claim 28 relates to a method of evaluating the effect of a medicine against asthenopia, which comprises the steps of: (1) (a) stimulating a ciliary muscle derived from a non-human test animal with a chemical stimulant to induce a first contraction of said ciliary muscle, and washing said ciliary muscle at a point where the contraction reaches a plateau; and (b) repeating step (a) 3 to 50 times and terminating at a point where said ciliary muscle shows a decrease of 50 $\pm$ 20% in the tension of muscle contraction, thereby producing *in vitro* asthenopia of the ciliary muscle; (2) contacting said ciliary muscle with a medicine in the presence of said chemical stimulant; and (3) comparing the decrease in the tension of the muscular contraction before and after contact with the medicine.

Distinctions between the Present Invention and the Cited Art

As a preliminary matter, Applicant points out that the translation of JP '225 utilized by the Examiner is inaccurate. Applicant believes that this inaccurate translation has resulted in a misunderstanding of the actual teachings of JP '225. The relevant portions of JP '225 are paragraphs [0022] and [0023]. Accordingly, to improve the understanding of JP '225, Applicant provides, attached hereto, an accurate translation of these two paragraphs.

Comparison between the Examiner's comments and the correct translation reveal some misunderstandings which Applicant will take this opportunity to clarify.

At page 3, lines 20-21 of the Office Action, the Examiner states that "[t]he ciliary muscle in JP '25 are first contracted or pretreated with compound A to induce astonopia." Applicant submits that the term "asonopia" is unknown. If the term is meant to refer to "asthenopia", then this statement is incorrect. Compound A in JP '225 is an agent for treating asthenopia by

relaxation of ciliary muscular contraction, not for inducing asthenopia. Thus, compound A never causes contraction of the ciliary muscles, but inversely has an inhibitory activity on ciliary muscular contraction.

Also, the subsequent statement in the Office Action that "[t]he step of adding KCl in JP '225 meets the instant step of contacting a "medicine" to the contracted muscles" is uncertain. KCl is an inducer of muscular contraction. In JP '225, KCl is evaluated to determine to what extent a muscular contraction due to KCl can be suppressed by pretreatment with compound A. Thus, KCl never corresponds to the present "medicine", but rather corresponds to a "chemical stimulant." According, the step of adding KCl never relates to contacting a medicine to the contracted muscles.

Further, the statement that "JP '225 describes that the rate of decrease in tension was about 22.9% which meets the limitations of the instant claims" is incorrect. The meaning of 22.9% in JP '225 is very different from the current understanding of the Examiner. In particular, 22.9% in JP '225 means that the contraction by KCl is suppressed by 22.(% by pretreatment with compound A. Whereas, in the present context, "a decrease of 50± 20% in the tension of muscle contraction" is the index showing the state of asthenopia, and it is evaluated how tension is changed upon contacting a medicine with such ciliary muscle in asthenopic condition. Therefore, the 22.9% value of JP '225 is unrelated to the decrease of 50± 20% in the tension of muscle contract of the present claims.

Once the differences between the present invention and JP '225 are evident, the correct conclusion is that there exists no *prima facie* case of obviousness. In specifics, the present invention is directed to a method for evaluating the effect of a medicine against asthenopia.

Importantly, the cilia muscle that is contacted with a medicine has been placed into an asthenopic state. In particular, by repeated stimulation of the ciliary muscle with a chemical stimulant, *in vitro* asthenopia is produced such that the ciliary muscle shows a decrease of 50 $\pm$ 20% in the tension of muscle contraction. This actual step of creating a fatigued ciliary muscle is unique to the present invention.

Indeed, none of the references cited by the Examiner either suggests or discloses such a step as employed by the presently claimed subject matter. The only reference which actually deals with asthenopia, although in a different way, is JP '225. However, significant differences exist between the present invention and JP '225. For instance, in JP '225, ciliary muscle is first treated with a compound that is an antagonist of KCl, that is, an inducer of muscular contraction. Thus, it is impossible for JP '225 to generate fatigued ciliary muscle by repeating a treatment with a chemical stimulant even a plurality of times.

More specifically, according to the present invention, the effect of a medicine on asthenopia is evaluated by measuring tension recovery of the muscular contraction of a ciliary muscle after administering the medicine to fatigued ciliary muscle (ciliary muscle having a decrease of 50 $\pm$ 20% in the tension of muscle contraction). In contrast, in JP '225, antagonism of a medicine against KCl is evaluated so the effects to be evaluated are very different from the effects to be evaluated in the present invention. Further, in JP '225, antagonism of a medicine against KCl is evaluated as the effects on asthenopia. However, this evaluation would not be appropriate in the present context since antagonism against KCl is merely as it is, not an index showing tension recovery of the muscular contraction of a ciliary muscle.

The Examiner has urged, during an interview conducted on March 28, 2007, that Applicant conduct comparative experiments. However, Applicant submits that comparative experiments are unnecessary and inappropriate given the large differences between the present invention and the cited art, for instance, JP '225. In fact, in order to perform comparative experiments, the case law indicates that Applicant should test the invention against the closest composition "actually taught in the reference". *Ex parte Westphal et al.*, 223 USPQ 630, 633 (Bd. Pat. App. & Int. 1983). Thus, Applicant could replicate the disclosure of JP '225. However, the next step would be to slightly modify the teachings of JP '225 to be within the scope of the present claims. However, such modifications involve so many changes for which no motivation exists in the prior art.

Thus, a request for a comparison is not rational. It is apparent that asthenopia is never caused by repetitious treatments with an antagonist against an inducer of muscular contraction (see JP '225). Thus, even without any comparative tests, it is evident that there exists no *prima facie* case of obviousness.

In view of the above, Applicant respectfully submits that the present claims define allowable subject matter. Accordingly, the Examiner is respectfully requested to withdraw all rejections and allow the currently pending claims.

If the Examiner has any questions or comments, please contact Craig A. McRobbie, Registration No 42,874 at the offices of Birch, Stewart, Kolasch & Birch, LLP.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for

any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

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Respectfully submitted,

By  #42,874

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PARTIAL ENGLISH TRANSLATION of

Japanese Patent Laid-Open No. Hei 7-133225

(Page 8, column 13, line 3 to column 14, line 6, [0022]-[0023])

[0022] "Pharmacological Test" An effect on contraction of ciliary muscle was examined using Inventive Compound A as a representative example of the compound of the present invention. Here, the experiment was carried out by using the following method in accordance with a literature by Lepple-Wienhues et al. (*Exp. Eye Res.*, 53, 33-38 (1991)).

(Experimental Method) Ciliary muscle removed from a bovine eyeball was suspended in a Magnus tube filled with a Krebs-Henseleit solution, oxygen containing 5% carbon dioxide gas was blown thereinto. After the equilibrium was reached, the ciliary muscle was pretreated with Inventive Compound A for 30 minutes before the addition of KCl, and the contraction induced by KCl was recorded isometrically.

[0023] (Results) By pretreating the ciliary muscle with Inventive Compound A, the control on the contraction of ciliary muscle induced by KCl was found, and its preventive ratio was 22.9%. Incidentally, even when a substance for inducing contraction of ciliary muscle was changed from KCl to carbachol, Inventive Compound A showed a preventive action to contraction of ciliary muscle. It was found out from the results that Inventive Compound has a preventive action on the contraction of ciliary muscle.